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McCune-Albright Syndrome: A Longitudinal Clinical Study of 32 Patients

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ABSTRACT

We report the diagnostic clinical features and their long term evolution in 32 patients with McCune-Albright syndrome. Patient data are made up of two periods: the first, classified as personal history, is from birth until the time when the diagnosis of McCune-Albright syndrome was made; the second, classified as clinical observation, is from the first observation until the end of follow up. The total duration of these two periods was 9.6 ± 2.9 yr; mean age at first observation was 5.7 yr (range 0.7-11 yr). The probability of manifesting main clinical signs according to age was calculated: almost all had skin dysplasia at birth, 50% probability of peripheral precocious puberty in females at 4 years and 50% of bone dysplasia at 8 years of age were found. Other clinical signs had diagnostic relevance when preceding the main signs leading to diagnosis of McCune-Albright syndrome even without specific genetic investigation. The most important clinical manifestations have different evolutions: skin lesions increase in dimensions according to body growth; precocious puberty in females evolves rapidly but periods of regression can be seen in some patients; bone dysplasia in most patients evolves with an increase both in the number of affected bones and in the severity of lesions.

KEY WORDS

McCune-Albright syndrome, cutaneous café-au-lait spots, bone fibrous dysplasia, precocious puberty

INTRODUCTION

The McCune-Albright syndrome (MCAS), a heterogeneous clinical condition[1-4], is caused by a postzygotic missense mutation in the gene codifying the alpha subunit of the Gs protein of the receptor system of most proteic hormones[5]. In MCAS patients, the abnormal Gs protein constitutively activates the receptors and the adenylacetyclase system causing autonomous cell proliferation and/or hormonal hypersecretion with consequent clinical features[4,6].

The classical form, more frequent in females, is defined by three main features: cutaneous café-au-lait spots, peripheral precocious puberty, and bone fibrous dysplasia; the nonclassical form consists of only two of these conditions[4,7]. In addition, hyperthyroidism, hypercortisolism, growth hormone (GH) and prolactin hypersecretion, liver, heart, lung and kidney dysfunctions have been described[6]. In some instances these additional clinical features can be regarded as severe illnesses in their own right. The cutaneous café-au-lait spots have different size, number, morphology and age of appearance and may indicate active melanocyte proliferation[8]. Peripheral precocious puberty is often atypical and

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characterized by alternate periods of rapid progression and regression of pubertal development. In females, menstrual bleeding may occur before breast modification. Often ovarian cyst growth and regression is seen as a sign of ovarian follicle hyperactivation[1-6,9]. Bone fibrous dysplasia is the consequence of hyperproliferation of preosteoblast cells and consists of osteolytic lacunar areas in long bones and sclerosis of the skull base[1-4,10]. Bone lesions can be monostotic or polyostotic and may be asymptomatic or cause pain and spontaneous fractures. These lesions occur mainly in femur, shinbone, ribs and facial bones and may cause deformity and limb dysmetria. Skull bone involvement may progress towards neurological damage, blindness, deafness, and vestibular dysfunctions [11,12].

Although MCAS has been known for many years, the long term outcome is largely unknown because data from longitudinal studies are scarce [3,13]. We report the results of a follow-up study of 32 MCAS patients of various ages in an attempt to clarify diagnostic clinical features and their long-term evolution.

PATIENTS AND METHODS

The data from 32 patients (27 females and 5 males, age range at MCAS diagnosis 0.7-11 yr) were collected from 11 Italian Pediatric and Pediatric Endocrinological Departments.

The study consisted of two periods: personal history from birth to the time of the first clinical observation when MCAS diagnosis was made, and subsequent clinical follow up. The duration of personal history (range 0.7-11 yr, mean 5.7 ± 2.8) and of clinical follow up (range 0.4-8.5 yr, mean 3.8 ± 2.3) varied among patients; total study duration ranged from 3-12 yr (mean 9.6 ± 2.8); 13 patients had reached the age of 12. The onset of clinical manifestations preceding MCAS diagnosis was recorded from personal history; the onset and evolution of further clinical signs from the time of MCAS diagnosis were evaluated at six month intervals by clinical observation.

Skin dysplasia was diagnosed on the basis of the typical irregularly shaped café-au-lait spots; their number and localization were recorded, and their shape and dimension were traced directly from the patient's body.

Precocious puberty was diagnosed in females, before the age of 8, on the basis of one or more of the following signs: breast enlargement and pubic hair development according to Tanner's stages[14], menarche and estrogenization of external genitalia. Precocious puberty was diagnosed in males, before the age of 9, on the basis of testicular volume greater than 4 ml according to Prader's orchidometer, androgenization of genitalia and pubic hair development, according to Tanner's standards[14]. In all cases autonomous gonadal hyperactivity was demonstrated by the rise of gonadal sex steroids (estradiol in females >20 pg/ml, testosterone in males >0.8 ng/ml) with concomitant suppression of gonadotropin secretion both basally and after GnRH stimulation (FSH and LH <2 mU/ml). Pelvic sonography with a real time ultrasound scanner equipped with a 3.5 or 5 MHz convex transducer was performed in 15 females at pubertal onset. Most patients were treated with drugs to block pubertal development (cyproterone acetate and/or testolactone in females, ketoconazole in males) and two females underwent ovarian cystectomy or ovariectomy to overcome drug resistant hyperestrogenism. Thus spontaneous evolution of puberty was not seen.

Bone dysplasia was looked for at the clinical level (pain, fractures, limb and skull deformities). Visual and hearing loss due to cranial nerve compression were also investigated in all patients with craniofacial bone dysplasia through visual acuity and field evaluations and audiometry.

The number, sites and morphology of bone lesions were recorded with radiological and/or scintigraphic imaging, generally performed at one year intervals. Severity of bone dysplasia was graded according to Feuillan's score[15] as follows: mild (absence of facial asymmetry, limb length discrepancy or gait abnormality); moderate (obvious facial/skull asymmetry, limb length discrepancy, no fracture or corrective surgery); marked (as in moderate, but with fracture and/or need for surgical correction).

When other endocrine or cellular hyperfunction was suspected on the basis of clinical and/or radiological data, the diagnosis of autonomous hyper-

function was made through specific hormonal and/or laboratory tests. FT_4, TSH, GH, estradiol, testosterone, LH, FSH were measured in blood at 8 a.m. Blood samples for ACTH and cortisol were collected at 8 a.m. and 10 p.m., while urinary cortisol was measured on 24-hour collection. Blood PRL profile was obtained every 30 min in the morning for 90 min. TSH was also measured 30 min after TRH bolus (100 μg, i.v.), GH 30, 60, 120, 180 min after oral glucose load (75 g), gonadotropins 20 and 40 min after GnRH bolus (100 μg, i.v.). All hormones were measured by specific RIAs. Standard thyroid, adrenal, pelvic and testis sonography was also performed. Renal loss of phosphates was demonstrated through standard biochemical measurements of phosphorus and creatinine in blood and 24-hour collected urine.

Statistical analysis of the age of onset of the three main clinical signs was performed according to Kaplan and Meier[16].

RESULTS

The clinical signs of the 32 patients with MCAS are reported in Table 1. Of the main clinical signs, precocious puberty was present in 30 patients (93.7%: 26 females, 4 males); bone dysplasia in 20 (62.5 %: 15 females, 5 males); skin dysplasia in 30 (93.7%: 25 females and 5 males). Peripheral hypercortisolism was seen in 2 patients (6.2%: 1 female, 1 male); the diagnosis was based on raised blood cortisol levels (>25 μg/dl) and concomitant reduced ACTH levels (<10 pg/ml) in repeated evaluation and raised 24-hour urinary cortisol values (>150 μg/24 h). Hyperprolactinemia was diagnosed in one patient (3.1%) on the basis of repeatedly raised prolactin levels (>800 μU/ml) during diurnal profile. Hyperthyroidism in another patient (3.1%) was based on reduced TSH (<0.2 μU/ml) and concomitant raised FT_4 (>15 pg/ml). GH hypersecretion in another patient (3.1%) was demonstrated by repeatedly elevated GH basal levels (>15 ng/ml), the lack of GH suppression after glucose oral load (>10 ng/ml) and raised IGF-I levels (>600 ng/ml). Hypophosphatemic rickets was seen in another patient with reduced blood phosphate levels (<3 mg/dl) and reduced tubular phosphate resorption (80%). Hepatocellular disease was diagnosed in another patient (3.1%), on the basis of persistently raised transaminase levels; bilirubin, lactate dehydrogenase, gamma-glutamyl transpeptidase and liver biopsy were all normal.

The typical irregularly shaped skin lesions (Fig. 1B) with various dimensions ranging from a few mm^2 to large areas, predominantly located around the midline were found on the trunk in 11 patients, on the limbs in six, on trunk and limbs in six, on the face, trunk and limbs in seven; 1-3 lesions were found in 19 patients, 4-6 in seven and >6 in four patients.

Of the 26 females with precocious puberty, 25 showed breast enlargement (22 at Tanner stage II and three at stage III) with hyperpigmented areolae and protruding nipples (Fig. 1A); seven also had pubic hair development (Tanner stage II); clinical signs of vulvar estrogenization were detected in 15 patients. Menarche occurred in 13 girls; in one without pubertal breast development (Table 2). Among the 15 patients who underwent pelvic sonography, 11 had single or multiple ovarian cysts (diameter range 1.8-3.5 cm).

The males with precocious puberty showed testes enlargement; two of them had pubic hair development (Table 2).

In the 20 patients with bone dysplasia (Fig. 1C-F, Tables 3, 4), a monostotic lesion was detected in one patient, while polyostotic lesions were present in 19. Skull base involvement was seen in 14 patients. Long bones were affected in 19 patients, short bones in nine and flat bones in 13 patients. At the end of follow up, the clinical severity of bone dysplasia, according to Feuillan's score, was mild in four patients, intermediate in three and severe in 13.

Among other clinical manifestations, hypercortisolism, hyperthyroidism and GH hypersecretion were suspected at the clinical level due to their typical signs and symptoms, while other conditions (hyperprolactinemia, hypophosphatemic rickets, hepatocellular disease) were not clinically evident and were detected only through specific laboratory investigations.

Main clinical signs appeared more frequently at specific ages, whereas others were seen at any age. The probability of main clinical signs with age is shown in Figure 2. Skin dysplasia probability is

TABLE 1

Clinical signs in 32 patients at diagnosis of McCune-Albright syndrome

PATIENT NUMBER	SEX	AGE	SKIN DYSPLASIA	PRECOCIOUS PUBERTY	BONE DYSPLASIA	OTHER
1	F	8.9	+	+	+	
2	M	5.1	+	+	+	
3	F	6	+	+	+	
4	F	7.8	+	+	+	Hyperprolactinemia
5	F	2.1	+	+		
6	F	4.6	+	+		
7	F	6.9	+	+		
8	F	3.1	+	+		
9	F	3.9	+	+		
10	F	2.1	+	+	+	Hypophosphoremic rickets
11	F	5.6	+		+	
12	F	7.8	+	+		
13	F	5	+	+		
14	M	6.5	+	+	+	Hyperthyroidism
15	F	3.6	+	+		
16	F	9	+	+	+	
17	F	1	+	+		
18	F	9.5	+	+	+	
19	M	9.8	+		+	
20	M	11	+	+	+	Hypercortisolism
21	F	2.5	+	+		
22	F	5.1	+	+	+	
23	F	7.4	+	+	+	
24	F	3.9	+	+	+	
25	F	7.4		+	+	
26	F	8	+	+		
27	F	0.7	+	+	+	Hypercortisolism,hepatic disease
28	F	2.8	+	+		
29	F	4	+	+	+	
30	F	5.1		+	+	
31	F	8.7	+	+	+	
32	M	9	+	+	+	GH hypersecretion

Fig.

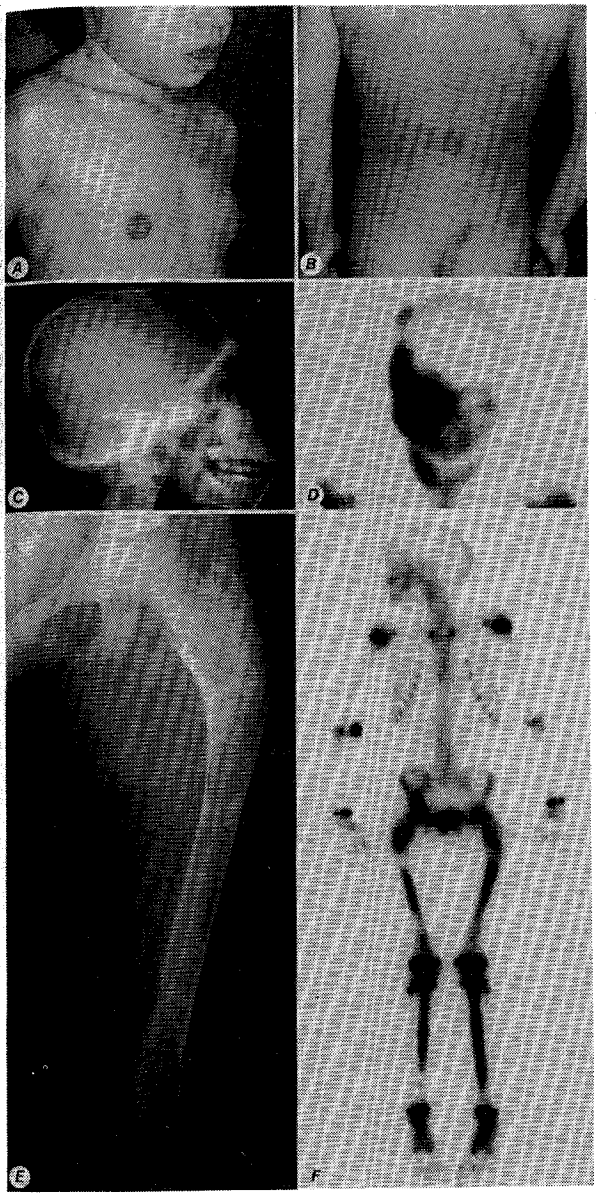

Fig. 1: **A.** Pubertal breast development with enlarged darkened areolas and protruding nipples. **B.** The typical irregularly shaped café-au-lait skin spots. **C.** Radiological features of skull bone dysplasia: diffuse skull basis sclerosis. **D.** Scintigraphic features of skull bone dysplasia: polyostotic lesion of right parietal, zygomatic and maxillar bones. **E.** Radiologic features of femur bone dysplasia: diffuse osteolitic lesions, fractrure and bowing of femoral neck. **F.** Total body scintigraphic features: high uptake in the pelvis and lower limbs.

very high from birth, and reaches its maximal value within the first 2 years of life; precocious puberty probability is relevant from the end of the first year of life and rises progressively up to the age of 8 in females and 9 in males; bone dysplasia probability is scarce between 2 and 4, rises between 4 and 8, and declines in the following 3 years.

Hypercortisolism and hepatocellular disease were found in the first year of life, while the other signs were diagnosed between 3 and 12 years of age (hypophosphatemic rickets in the 4th year of life, hyperthyroidism in the 7th, hyperprolactinemia in the 8th, GH hypersecretion in the 12th).

During follow-up, the number and morphology of skin lesions did not change. Changes in the number, localization and symptoms of bone dysplasia were observed in 12 patients (Tables 3, 4): in two patients (#16, 29) both the number of lesions and the clinical severity progressed; in nine patients (#1, 3, 4, 14, 20, 22, 23, 27, 30) only the number of lesions increased; in one patient (#2) only the clinical severity worsened. Eight patients (#10, 11, 18, 19, 24, 25, 31, 32) did not show bone dysplasia progression; of these seven had a clinically severe form of dysplasia and only one (#18) an intermediate form.

DISCUSSION

McCune-Albright syndrome is caused by a post-zygotic mutation of embryonic somatic cells with consequent mosaicism. Therefore its clinical expression depends on the number of mutated cells and the affected organs. MCAS patients may show a heterogeneous and complex clinical picture, with early or late onset, and slow or quick evolution toward more severe forms with wider involvement of additional organs. Our series confirms this clinical variability: the classical form is the most frequent, but non-classical forms and additional hepatocellular, adrenal and hypophyseal diseases were also observed.

Even with the possible diagnostic bias of having incorrectly recorded retrospective data, this study describes the onset and the evolution of clinical signs in a cohort of pediatric patients.

Neonatal onset was seen in some patients, with café-au-lait spots, hypercortisolism and hepato-

TABLE 2

Onset of pubertal signs in 30 patients with McCune-Albright syndrome

PATIENTS NUMBER	SEX	AGE (yrs) AT DIAGNOSIS OF MCAS	AGE (yrs) AT ONSET OF PUBERTAL SIGNS	BREAST STAGE	MENARCHE	TESTICULAR VOLUME (ml)	PUBIC HAIR STAGE
1	F	8.9	0.5	II			I
2	M	5.1	5			5	I
3	F	6	4	II			I
4	F	7.8	0.5	II	+		I
5	F	2.1	2	III			I
6	F	4.6	4.5	II	+		I
7	F	6.9	6	II			II
8	F	3.1	3	II	+		I
9	F	3.9	1.6	II	+		II
10	F	2.1	0.4	I	+		I
12	F	7.8	6.8	II			I
13	F	5	5	II			I
14	M	6.5	6.6			12	I
15	F	3.6	3.2	II	+		II
16	F	9	7.5	II	+		I
17	F	1	0.9	II			I
18	F	9.5	5	II	+		I
20	M	11	11			5	IV
21	F	2.5	1.5	II			I
22	F	5.1	5.1	II	+		I
23	F	7.4	4	II			I
24	F	3.9	3.9	II	+		II
25	F	7.4	5	II			I
26	F	8	7	II			I
27	F	0.7	0.7	III	+		II
28	F	2.8	2.8	III	+		II
29	F	4	0.4	II	+		II
30	F	5.1	3	II			I
31	F	8.7	6	II			I
32	M	9	9			4	II

pathy. To date four patients with early manifesting hypercortisolism have been described[1,10], to which our two patients must be added. The finding of early ACTH-independent hypercortisolism should be considered in the diagnosis of MCAS[17,18].

In some females the onset consisted of extremely early signs of precocious puberty with telarche and vulvar estrogenization often associated with menarche and pubic hair development. In males precocious puberty developed later, between 4 and 9 years of age, with testis enlargement, genitalia androgenization and sometimes pubarche.

In rare cases the first clinical signs were those of bone dysplasia appearing after the sixth year of life with bone pain, gait abnormalities and limb deformities.

Other clinical manifestations were seen at any age; they were predominantly due to endocrine hyperfunction and not to cell proliferation. Abnormalities of the thyroid are the second most common form of endocrinopathy in MCAS[3,4]. Several thyroid disorders have been described in association with MCAS, including nodular goiter, cystic lesions of the thyroid and hyperthyroidism[19].

TABLE 3

Bone dysplasia: age and signs at onset (a) and at the end of follow up (b) in 20 patients with McCune-Albright syndrome

PATIENT NUMBER		AGE (yrs)	LONG BONES	SHORT BONES	FLAT BONES
1	a	5	femora		skull base
	b	12	femora	carpus	skull base, skullcup
2	a	5	femora	metacarpal bone,phalanges	skull base, skullcup, pelvis
	b	12	femora	metacarpal bone,phalanges	skull base, skullcup, pelvis
3	a	6	femora	left hand phalanges	skull
	b	9.2	femora,tibias	left hand phalanges	skull base, skullcup, ribs
4	a	7.9	left femur		
	b	9.8	femora,tibias		
10	a	2.1	femora,humeri		skull base, skullcup,left scapula and ribs,pelvis
	b	3	femora,humeri		skull base, skullcup,left scapula and ribs,pelvis
11	a	5.7	left femur,left tibia	ankle bone	
	b	7.3	left femur,left tibia	ankle bone	
14	a	6	femora,tibias,humeri,ulnas	vertebra	skull base, pelvis
	b	12	femora,tibias,humeri,ulnas	vertebra	skull base, pelvis
16	a	6	femora,tibias		
	b	12	femora,tibias,humeri,ulna	carpus, metacarpal bone, phalanges	ribs, pelvis
18	a	9.6	femora		
	b	12	femora		
19	a	3	right humerus		
	b	11.6	right humerus		
20	a	11	femora,humeri		skull base, pelvis
	b	12	femora,humeri		skull base, scapula
22	a	5.2	femora		skull base, pelvis
	b	12	femora,tibias,calfbones		skull base, skullcup, ribs
23	a	7.5	right femur and calf bone, left humerus	left carpus, metacarpal bone	skull base
	b	12	right femur and calf bone, left humerus	left carpus, metacarpal bone	skull base, skullcup
24	a	3.9	right femur, left tibia,calf bone,	right foot phalanges	skull base, pelvis
			and humerus		
	b	10.9	right femur, left tibia,calf bone	right foot phalanges	skull base, pelvis
			and humerus		
25	a	7.5	femora,right calf bone and humerus,	metacarpal bone	skull base
			left tibia and ulna		
	b	12	femora,right calf bone and humerus,	metacarpal bone	skull base
			left tibia and ulna		
27	a	3.4	femora, tibias, left humerus	metacarpal bone	skullcup, left scapula
	b	4.9	femora, tibias, left humerus and radius	metacarpal bone	skull base,skullcup, left scapula, ribs
29	a	4	left femur		skull base, skullcup
	b	12	left femur,tibia and humerus, right femur		skull base, skullcup, left ribs
			and calf bone		
30	a	5.2	femora		
	b	9	femora, tibias, right humerus		skull base, right pelvis
31	a	8.8	left femur and tibia		
	b	12	left femur and tibia		
32	a	9.1			skull base, skullcup
	b	12			skull base, skullcup

In our series only one patient with hyperthyroidism was found, probably because minor thyroid dysfunctions were overlooked.

GH excess has been increasingly recognized in MCAS both alone and in association with prolactin hypersecretion and pituitary adenoma[3,4,20,21]. In the

TABLE 4

Bone dysplasia: age and severity at onset (a) and at the end of follow up (b) in 20 patients with McCune-Albright syndrome

		AGE (yrs)		a		b
CASES	SEX	AT MCAS DIAGNOSIS	AGE (yrs)	SEVERITY	AGE (yrs)	SEVERITY
1	F	8.9	5		12	Severe
2	M	5.1	5	Intermediate	12	Severe
3	F	6	6	Mild	9.2	Mild
4	F	7.8	7.9	Intermediate	9.8	Intermediate
10	F	2.1	2.1	Severe	3	Severe
11	F	5.6	5.7	Severe	7.3	Severe
14	M	6.5	6	Intermediate	12	Intermediate
16	F	9	6	Mild	12	Severe
18	F	9.5	9.6	Intermediate	12	Intermediate
19	M	9.8	3	Severe	11.6	Severe
20	M	11	11	Severe	12	Severe
22	F	5.1	5.2	Mild	12	Mild
23	F	7.4	7.5	Mild	12	Mild
24	F	3.9	3.9	Severe	10.9	Severe
25	F	7.4	7.5	Severe	12	Severe
27	F	0.7	3.4	Mild	4.9	Mild
29	F	4	4	Mild	12	Severe
30	F	5.1	5.2	Severe	9	Severe
31	F	8.7	8.8	Severe	12	Severe
32	M	9	9.1	Severe	12	Severe

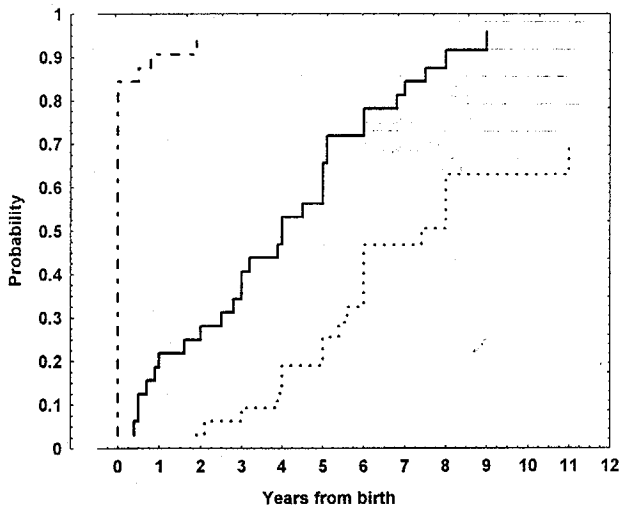

Fig. 2: Probability of major clinical signs (skin dysplasia, peripheral precocious puberty, bone dysplasia) in 32 patients with MCAS according to the age of onset.

patient affected by GH hypersecretion, body and skull overgrowth could be attributed to the combined effects of GH excess, precocious puberty and bone dysplasia.

Hypophosphatemic rickets is a less frequent finding in MCAS[3,4], although altered renal adenylate-cyclase activity has been seen in a number of MCAS patients[22].

In one patient, mild signs of hepatocellular dysfunction were detected at birth and later confirmed by the typical R201H mutation in the liver biopsy (A. Shenker, personal communication). This finding is in accordance with the suggestion that genetic derangement is the cause of hepatobiliary disease in MCAS patients[6].

Each main clinical sign had different evolution: café-au-lait skin lesions did not change in color, shape and number, and their dimensions increased

according to body growth; in females, precocious puberty usually started with sudden and massive estrogenization and evolved rapidly, but in some patients periods of regression could also be seen; in most patients bone dysplasia was already present in a severe form at diagnosis and evolved with an increase both in the number of affected bones and the severity of lesions. Neither in our experience nor in the literature has bone dysplasia regression been seen[3].

Hypercortisolism was singular in its evolution: it regressed within the first years of life in the two patients described here. The other endocrine and non-endocrine signs showed a slow chronic progression despite specific treatments, such as metimazole in thyrotoxicosis, octreotide in GH hypersecretion, and phosphates in hypophosphatemia .

The relevance of our study consists of the calculation of the probability of the main clinical signs according to age: almost complete skin dysplasia expression at birth; 50% probability of precocious puberty in females at 4 years and 50% bone dysplasia probability at 8 years of age.

Some suggestions on the McCune-Albright syndrome at pediatric age can be put forward: early diagnosis is possible and recommended. Isolated skin dysplasia has scarce diagnostic value since about 10% of normal children have similar skin café-au-lait spots[13]. When additional signs of autonomous endocrine hyperfunction (peripheral precocious puberty, Cushing's syndrome, hyperthyroidism, GH and prolactin hypersecretion) or of cell proliferation (bone dysplasia, idiopathic hepatobiliary disease, thymic hyperplasia, gastrointestinal polyps) are seen, MCAS must be suspected. The diagnostic confirmation may be obtained from molecular studies of Gs protein mutations[5,6].

Early diagnosis is necessary to formulate correct prognostic hypotheses and to plan adequate therapeutic measures. Sometimes it is better to wait for spontaneous regression of the symptoms before starting specific treatment. Indeed, precocious puberty progression both in males and females can be slowed with drugs, such as ketoconazole and testolactone, and even surgical procedures such as ovarian cystectomy and ovariectomy[4,7,15]. Moderate and severe forms of bone dysplasia may be treated, as soon as detected, with bisphosphonates, which reduce bone pain and fractures and seem to slow the evolution of bone disease[7].

Further controlled longitudinal studies are needed to clarify the long-term outcome of this protean illness.

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